



lissencephaly with cerebellar hypoplasia

Lissencephaly with cerebellar hypoplasia (LCH) affects brain development, resulting in the brain having a smooth appearance (lissencephaly) instead of its normal folds and grooves. In addition, the part of the brain that coordinates movement is unusually small and underdeveloped (cerebellar hypoplasia). Other parts of the brain are also often underdeveloped in LCH, including the hippocampus, which plays a role in learning and memory, and the part of the brain that is connected to the spinal cord (the brainstem).

Individuals with LCH have moderate to severe intellectual disability and delayed development. They have few or no communication skills, extremely poor muscle tone (hypotonia), problems with coordination and balance (ataxia), and difficulty sitting or standing without support. Most affected children experience recurrent seizures (epilepsy) that begin within the first months of life. Some affected individuals have nearsightedness (myopia), involuntary eye movements (nystagmus), or puffiness or swelling caused by a buildup of fluids in the body's tissues (lymphedema).

Frequency

LCH is a rare condition, although its prevalence is unknown.

Genetic Changes

LCH can be caused by mutations in the *RELN* or *TUBA1A* gene. The *RELN* gene provides instructions for making a protein called reelin. In the developing brain, reelin turns on (activates) a signaling pathway that triggers nerve cells (neurons) to migrate to their proper locations. The protein produced from the *TUBA1A* gene is also involved in neuronal migration as a component of cell structures called microtubules. Microtubules are rigid, hollow fibers that make up the cell's structural framework (the cytoskeleton). Microtubules form scaffolding within the cell that elongates in a specific direction, altering the cytoskeleton and moving neurons.

Mutations in either the *RELN* or *TUBA1A* gene impair the normal migration of neurons during fetal development. As a result, neurons are disorganized, the normal folds and grooves of the brain do not form, and brain structures do not develop properly. This impairment of brain development leads to the neurological problems characteristic of LCH.

Inheritance Pattern

When LCH is caused by mutations in the *RELN* gene, the condition is inherited in an autosomal recessive pattern, which means both copies of the gene in each cell have mutations. The parents of an individual with an autosomal recessive condition each

carry one copy of the mutated gene, but they typically do not show signs and symptoms of the condition.

When LCH is caused by mutations in the *TUBA1A* gene, the condition is inherited in an autosomal dominant pattern, which means one copy of the altered gene in each cell is sufficient to cause the disorder. Most of these cases result from new mutations in the gene and occur in people with no history of the disorder in their family.

Other Names for This Condition

- LCH
- LIS2
- LIS3
- lissencephaly 2
- lissencephaly 3
- lissencephaly syndrome, Norman-Roberts type
- Norman-Roberts syndrome

Diagnosis & Management

Genetic Testing

- Genetic Testing Registry: Lissencephaly 2
<https://www.ncbi.nlm.nih.gov/gtr/conditions/C0796089/>
- Genetic Testing Registry: Lissencephaly 3
<https://www.ncbi.nlm.nih.gov/gtr/conditions/C1969029/>

General Information from MedlinePlus

- Diagnostic Tests
<https://medlineplus.gov/diagnostictests.html>
- Drug Therapy
<https://medlineplus.gov/drugtherapy.html>
- Genetic Counseling
<https://medlineplus.gov/geneticcounseling.html>
- Palliative Care
<https://medlineplus.gov/palliativecare.html>
- Surgery and Rehabilitation
<https://medlineplus.gov/surgeryandrehabilitation.html>

Additional Information & Resources

MedlinePlus

- Encyclopedia: Cerebellum--Function (image)
<https://medlineplus.gov/ency/imagepages/18008.htm>
- Health Topic: Brain Malformations
<https://medlineplus.gov/brainmalformations.html>
- Health Topic: Epilepsy
<https://medlineplus.gov/epilepsy.html>

Genetic and Rare Diseases Information Center

- Lissencephaly 2
<https://rarediseases.info.nih.gov/diseases/3277/lissencephaly-2>

Additional NIH Resources

- National Institute of Neurological Disorders and Stroke: Epilepsy Information Page
<https://www.ninds.nih.gov/Disorders/All-Disorders/Epilepsy-Information-Page>
- National Institute of Neurological Disorders and Stroke: Lissencephaly Information Page
<https://www.ninds.nih.gov/Disorders/All-Disorders/Epilepsy-Information-Page>

Educational Resources

- Cleveland Clinic
<http://my.clevelandclinic.org/health/articles/lissencephaly>
- Disease InfoSearch: Lissencephaly 2
<http://www.diseaseinfosearch.org/Lissencephaly+2/4270>
- Disease InfoSearch: Lissencephaly 3
<http://www.diseaseinfosearch.org/Lissencephaly+3/8762>
- Kennedy Krieger Institute: Brain Malformations
<https://www.kennedykrieger.org/patient-care/diagnoses-disorders/brain-malformations>
- MalaCards: lissencephaly with cerebellar hypoplasia
http://www.malacards.org/card/lissencephaly_with_cerebellar_hypoplasia
- Orphanet: Lissencephaly syndrome, Norman-Roberts type
http://www.orpha.net/consor/cgi-bin/OC_Exp.php?Lng=EN&Expert=89844

Patient Support and Advocacy Resources

- American Association on Intellectual and Developmental Disabilities (AAIDD)
<http://aaidd.org/>
- National Ataxia Foundation
<http://www.ataxia.org/>
- National Organization for Rare Disorders (NORD): Lissencephaly
<https://rarediseases.org/rare-diseases/lissencephaly/>
- Resource List from the University of Kansas Medical Center
<http://www.kumc.edu/gec/support/lissence.html>

ClinicalTrials.gov

- ClinicalTrials.gov
<https://clinicaltrials.gov/ct2/results?cond=%22lissencephaly+with+cerebellar+hypoplasia%22+OR+%22Lissencephaly%22+OR+%22Neuronal+Migration+Disorders%22>

Scientific Articles on PubMed

- PubMed
<https://www.ncbi.nlm.nih.gov/pubmed?term=%28%28lissencephaly%5BTIAB%5D%29+AND+%28cerebellar+hypoplasia%5BTIAB%5D%29%29+AND+english%5Bla%5D+AND+human%5Bmh%5D+AND+%22last+3600+days%22%5Bdp%5D>

OMIM

- LISSENCEPHALY 2
<http://omim.org/entry/257320>
- LISSENCEPHALY 3
<http://omim.org/entry/611603>

Sources for This Summary

- Chang BS, Duzcan F, Kim S, Cinbis M, Aggarwal A, Apse KA, Ozdel O, Atmaca M, Zencir S, Bagci H, Walsh CA. The role of RELN in lissencephaly and neuropsychiatric disease. *Am J Med Genet B Neuropsychiatr Genet.* 2007 Jan 5;144B(1):58-63.
Citation on PubMed: <https://www.ncbi.nlm.nih.gov/pubmed/16958033>
- Gressens P. Pathogenesis of migration disorders. *Curr Opin Neurol.* 2006 Apr;19(2):135-40. Review.
Citation on PubMed: <https://www.ncbi.nlm.nih.gov/pubmed/16538086>
- Hong SE, Shugart YY, Huang DT, Shahwan SA, Grant PE, Hourihane JO, Martin ND, Walsh CA. Autosomal recessive lissencephaly with cerebellar hypoplasia is associated with human RELN mutations. *Nat Genet.* 2000 Sep;26(1):93-6. Erratum in: *Nat Genet* 2001 Feb;27(2):225.
Citation on PubMed: <https://www.ncbi.nlm.nih.gov/pubmed/10973257>

- Kumar RA, Pilz DT, Babatz TD, Cushion TD, Harvey K, Topf M, Yates L, Robb S, Uyanik G, Mancini GM, Rees MI, Harvey RJ, Dobyns WB. TUBA1A mutations cause wide spectrum lissencephaly (smooth brain) and suggest that multiple neuronal migration pathways converge on alpha tubulins. Hum Mol Genet. 2010 Jul 15;19(14):2817-27. doi: 10.1093/hmg/ddq182. Epub 2010 May 12.
Citation on PubMed: <https://www.ncbi.nlm.nih.gov/pubmed/20466733>
Free article on PubMed Central: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2893812/>
- Ross ME, Swanson K, Dobyns WB. Lissencephaly with cerebellar hypoplasia (LCH): a heterogeneous group of cortical malformations. Neuropediatrics. 2001 Oct;32(5):256-63.
Citation on PubMed: <https://www.ncbi.nlm.nih.gov/pubmed/11748497>
- Zaki M, Shehab M, El-Aleem AA, Abdel-Salam G, Koeller HB, Ilkin Y, Ross ME, Dobyns WB, Gleeson JG. Identification of a novel recessive RELN mutation using a homozygous balanced reciprocal translocation. Am J Med Genet A. 2007 May 1;143A(9):939-44.
Citation on PubMed: <https://www.ncbi.nlm.nih.gov/pubmed/17431900>

Reprinted from Genetics Home Reference:

<https://ghr.nlm.nih.gov/condition/lissencephaly-with-cerebellar-hypoplasia>

Reviewed: August 2013

Published: March 21, 2017

Lister Hill National Center for Biomedical Communications

U.S. National Library of Medicine

National Institutes of Health

Department of Health & Human Services